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10/551,692	09/30/2005	Toshiki Nishizawa	NISHIZAWA3	5980

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,692	NISHIZAWA, TOSHIKI	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *8,9 and 12-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-20 are pending.

2. Applicant's election with traverse of Group I, claims 1-7, 10 and 11 drawn to a polypeptide comprising of least 1 cell attachment motif or 1 or more cell adhesion molecules plus a T cell epitope linked to a B cell epitope, RGD and streptococcus mutans serotype C strain as the species filed on 3/22/07, is acknowledged.

Applicant's traversal is on the grounds that present application is a 371 application, and under PCT unity of invention, a polypeptide and a polynucleotide encoding the polypeptide are considered to share a special technical feature. Furthermore, host organisms containing the novel polynucleotide would also necessarily share the same special technical feature. This is not found persuasive because the different composition of Groups I-X do not have a common core structure or function. In addition, the different composition of Group I do not have a common core structure or function because there is no 1:1 correlation between DNA and protein. The products are a family of proteins not one particular protein (see PCT Rule 13.2 and example 17 of Annex B) in MPEP. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 8-9, 12-20 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-7, 10 and 11 are under examination as they read on a polypeptide comprising of least 1 cell attachment motif or 1 or more cell adhesion molecules plus a T cell epitope linked to a B cell epitope, RGD and streptococcus mutans serotype C strain as the species.

5. Applicant's IDS, filed 10/10/06, is acknowledged.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-7 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NOs: 32-35 and 38-39 and a composition thereof as immunological adjuvant for the induction of antibodies, does not reasonably provide enablement for the polypeptides as claimed in claims 17 and 10-11. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to how to make and use the invention commensurate in scope with these claims.

The specification disclosure does not enable one skilled in the art to practice the invention without any undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Besides, SEQ ID NO: 32-35 and 38-39, which comprise the adhesion attachment motif RGD (SEQ ID NO: 2) and the B cell epitope of streptococcus mutans serotype C strain (SEQ ID NO:1), the overlapping multiagreteope type T cell epitope (SEQ ID NO 19) and the spacer/linker KK. The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only the overlapping multiagretope type T cell epitope (SEQ ID NO:2) and the T1 peptide (derived from HIV IIIB gp120) in the N-terminal region of the polypeptide and the streptococcus mutans serotype C strain (SEQ ID NO:1), OVAp (SEQ ID NO: 38-39) in the C-terminal region of the polypeptide, with RGD or RED, YIGSR attachment motifs (e.g., page 60 at lines 23-25), which positions via a lnker peptide inserted between the two amino acid of the T- B-cell epitope (se examples 8-9 in particular). The instant claims encompass in their breadth *any* "attachment motifs/adhesive molecules", any amino acid sequence of any "T cell epitope" or "B cell epitope".

The specification discloses on page 11, lines 9-10, that the attachment motifs enhance the production of specific antibodies. The specification on page 11, lines 1-8 and page 28, lines 9-13 discloses cell attachment motifs, such as RGD, RED, LDV, PHSRN, PKK, DGEA, IGSR, IKVAV, IRVVM and RFYVVMWK. However, the specification, table 7, shows that RED and HAV did not enhance the production of antibody (see row 9-10 in particular). Further, Yano *et al* (Vaccine 22: 237-243, IDS ref.) teach the effect of cell attachment motifs on the enhancement of antibody production. Yano *et al* teach that DED, DRE and HAV when added to the peptide, there was no appreciable boost in antibody production, (see page 239, the bridging sentence between col. 1 and col. 2, Fig. 1). Yano *et al* teach that despite similar chemical and physical properties, between RED, DRE and DED, only the RED motif enhanced immunogenicity of the peptide. Yano *et al* concluded that there are sequence-specific differences in the enhancing effects of the attachment motif (see page 241, col., 1 under Discussion). Further, it is noted that the RGD motifs are well known in the art at the time of the invention, and RGD motifs are bound by surface integrin receptors. However, the specialized medical literature contains hundreds of reports indicating many RGD-related peptides with different activities and different efficacy. The use of peptides containing the RGD motif has been proposed in several pathologic conditions, with different activities including anti-angiogenesis, anti-thrombotic and anti-metastatic action. The specification does not provide guidance that an RGD motif with one

activity can be use for another activity with the same efficacy.

Further, the skill in the art would doubt that the claimed *polypeptide* would work with any T- or B- cell epitope in addition with attachment motifs. The Examiner points that Maier *et al* in J. Neuroscience (26(18):4717-4728, 2006) cast serious doubt on the theory that a polypeptide containing three-amino acid RGD-cell attachment motif at the N terminus, would increase immunogenicity and replace the use of adjuvant in combination with different immunogen. Maier *et al* uses the peptide-immunogens with tandem repeat of two lysine-linked Aβ1-15sequences to across-species active T1 T-helper-cell epitope and each with the addition of RGD, RGD-$A\beta_{1-15}$-KK-$A\beta_{1-15}$ (R2xAβ1-15) and T1-RGD-KK-$A\beta_{1-5}$ (T1-R-Aβ1-15). Maier et al teach that addition of the RGD motif to the immunogens did not substantially increase antibody titers in long-term immunizations and was not able to replace the use of adjuvants as described for other immunogens in Yano et al 2003. Maier *et al* teaches that splenocytes from R-2XAβ1-15 immunized mice shoed higher SI (stimulation index) after restimulation with R-2XAβ1-15 compared with 2XAβ1-15, suggesting that RGD contributes to the secondary structure of the 2XAβ1-15-containing immunogens by creating a new, slightly different T-cell epitope. Maier et al concluded that regardless of the mechanisms, RGD-containing peptides did not increase Aβ antibody levels but did accelerate antibody production (see page 4725, bridging ¶ between col. 1 &2). Thus, the clinical benefits from increasing immunogenicity and replacing the use of adjuvant with any immunogen (T- B-cell epitope) are still not certain, casting some doubts on this therapeutic approach. The intended uses of the RGD-containing immunogens are fraught with uncertainties.

The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the a) attachment motifs/adhesive molecules, b) T cell epitope c) B cell epitope. Applicant is relying upon certain biological activities and the disclosure of two species of T cell epitope (OMP and T1) and two species of B cell epitope (streptococcus mutans serotype C strain of SEQ ID NO: 1 and OVp) and three adhesion motifs (RGD, RED and YIGSR) to support an entire genus. The claims read on yet to be identified T- B- cell epitopes and adhesion motifs. The T cell epitope sequence reads on both MHC class I and MHC class II. Therefore, absent the ability to predict which of these polypeptides would function as claimed for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. Claims 1-7 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of polypeptide of SEQ ID NO: 32-35 and 38-39 and a composition thereof.

Applicant is not in possession of the polypeptides claimed in claim 1-7 and 10-11.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (attachment motifs or T-, B- cell epitopes, antigenic protein causing disease, antigenic protein) to describe the claimed genus, nor does it provide a description of structural features that are common to species (attachment motifs or T-, B- cell epitopes, antigenic protein causing disease, antigenic protein). The specification provides no structural description of attachment motifs or T-, B- cell epitopes other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed peptide looks like. The specification's disclosure is inadequate to describe the claimed genus of attachment motifs or T-, B- cell epitopes, antigenic protein causing disease, antigenic protein.

Applicant has disclosed only amino acid of SEQ ID NO: 32-35 and 38-39; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 3-6 and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over French publication 2,776,926 (1998) in view of Okada et al (Cancer Res. 61:7913-7919, 2001).

The `926 publication teaches lipopeptides comprising a lipid part, a first spacer, a T auxiliary epitope, a second spacer, and a CTL epitope (see page 9). The T auxiliary can be a multivalent peptide from tetanus toxin (see page 11). The CTL epitope of a protein presented by a tumor cell, HIV protein of the hepatitis B virus or the papillomavirus, or even from the protein P53 (see page 11). The spacer can be SS or GR, AAA, RGR, (see page 14, under Lipopeptide No. 1, 2 and 3). The `926 publication further teaches the these lipopeptides can be store in solution and diluted extemporaneously for injection in a buffer aqueous solution (see page 4, 3rd ¶).

The claimed invention differs from the reference teachings only by the recitation of attachment motifs or adhesive molecules in claim 1, RGD in claim 3.

Okada et al teach that efficient antigen gene transduction using Arg-Gly-Asp (RGD) fiber-mutant adenovirus vectors can potentiate antitumor vaccine efficacy and maturation of murine dendritc cells. Okada et al teach effective induction of antigen-specific CTL response is more important for antitumor immunity than the enhancement of the humoral immune response (see page 7916, under Discussion). Okada et al teach that a number of tumor-associated antigens have been structurally and genetically defined and dendritic cells have been genetically engineered to present antigenic peptides via MHC class I and possibly class II molecules (see page 7913 2nd col., 1st ¶ in particular). Finally, Okada et al teach that DCs can process intracellular and internalized antigens, present them to naïve $CD4^+$ and $CD8^+$ T cells, and consequently generate a strong immune response against these antigens, DC-based immunotherapy has been studies widely as a potential approach for vaccinating against or treating cancers (page 7913, 2nd col., 1st sentence in particular).

Given that DCs can process intracellular and internalized antigens present them to naïve $CD4^+$ and $CD8^+$ T cells, and consequently generate a strong immune response against these antigens, DC-based immunotherapy has been studies widely as a potential approach for vaccinating against or treating cancers, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the lipid part of the lipopeptides taught by the `926 publication with the RGD system taught by Okada et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because to efficiently transducer the antigen peptides taught by the '926 publication and induce antigen-specific immune responses by vaccination.

Claim 11 is included because the resultant RGD-polypeptide is also an antigenic protein.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claims 2 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over French publication 2,776,926 (1998) in view of Okada et al (Cancer Res. 61:7913-7919, 2001) as applied to claims 1, 3-7 and 10-11 above, and further in view of Oishi et al, (2001, IDS ref.).

The teachings of '926 publication and Okada et al have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the linker peptide is KK in claim 2 and that the B cell epitope is streptococcus mutans serotype C strain in claim 7.

Oishi et al teach the effect of amino acid spacers on the antigenicity of dimeric peptide-indcuing cross-reacting antibodies to a cell surface protein antigen of streptococcus mutans. Oishi et al teach the synthetic peptide vaccine for dental caries was identified as a unique 13-mer peptide named Pac(365-377), TYEAALKQYEADL, as a minimum peptide inducing cross-inhibiting antibodies to a cell surface protein antigen (Pac) of streptococcus mutans. Oishi et al further teach that significant augmentation of antigenicity was obtained in all of the dimeric unit peptides with spacers, especially for lysine spacers. Oishi et al teaches that results revealed that the di-lysine spacer can be more effective in inducing the cross-reacting antibodies to rPac (see abstract in particular). Oishi et al concluded that the tandem repeat of the unit peptide with di-lysine spacer is very effective for improving the unit peptide antigenicities. Moreover, the di-lysine spacer is considered extremely useful to construct a multivalent peptide vaccine.

For skilled artisan who is interested in developing vaccine for dental caries, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the spacer part and the CTL part of the lipopeptides taught by the '926 publication with the KK spacer and TYEAALKQYEADL taught by Oishi et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the PAc peptide induces cross-inhibiting antibodies to a cell surface protein antigen PAc and the tandem repeat of the unit peptide with di-lysine spacer is very effective for improving the unit peptide antigenicities.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 9, 2007

Maher Haddad

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